

Radiation Therapy for Liver Tumors

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Radiation therapy (RT) has traditionally had a limited role in the treatment of liver tumors, primarily because of the low whole-organ tolerance of the liver to radiation. When radiation is applied to the entire liver, RT doses of 30 to 33 Gy carry about a 5% risk of radiation-induced liver disease (RILD). The risk rises rapidly, such that by 40 Gy, the risk is approximately 50% (1). Considering that most solid tumors require RT doses higher than 60 Gy to provide a reasonable chance for local control, it is not surprising that whole-organ liver RT provides only a modest palliative benefit rather than durable tumor control (2).

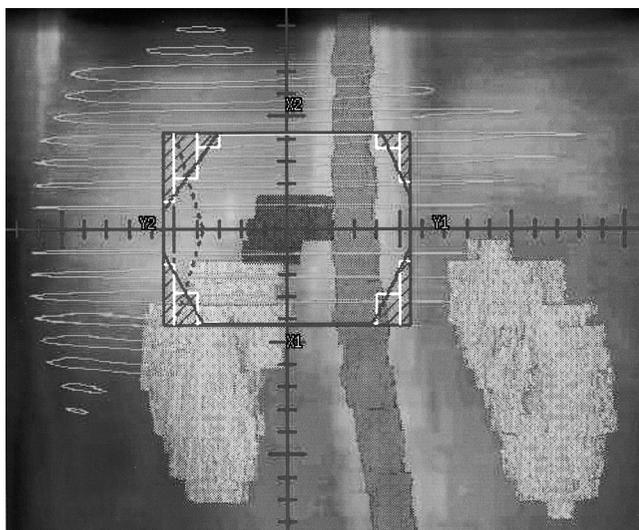
Hepatic dysfunction after RT frequently has been designated “radiation hepatitis,” but radiation-induced liver disease (RILD) is a more appropriate term because there is no histological evidence of hepatitis (3). Patients who suffer from this complication present with painful hepatomegaly and anicteric ascites from 3 weeks to 3 months after the completion of RT, without evidence of progressive cancer within the liver. The alkaline phosphatase is markedly elevated, out of proportion to modest increases in the transaminases or bilirubin. A biopsy of the liver demonstrates veno-occlusive disease pathologically identical to that resulting from several insults. Although most patients with RILD can recover with supportive care, some patients develop overt liver dysfunction, with coagulopathies, thrombocytopenia, and mental status changes, resulting in death.

In this chapter, we review the traditional role of external beam radiation therapy for hepatic tumors. Following this review, the technical aspects of three-dimensional conformal radiation treatment planning are discussed and the results of the published clinical trials are summarized. Finally, we discuss new directions for improvements with more advanced external beam radiation techniques such as intensity-modulated radiation therapy (IMRT).

THREE-DIMENSIONAL CONFORMAL AND INTENSITY-MODULATED TREATMENT PLANNING

Prior to the development of three-dimensional conformal radiation treatment planning (RTP), treatment of the liver with high doses was limited to clinical “guesswork” because traditional treatment planning was unable to localize the intrahepatic tumor with confidence, plan the optimal beam arrangement, and calculate the volume of normal liver that would be left untreated. Traditional RTP was performed using a manually obtained outline of the external surface of the patient at the center of the treatment area. The locations of the treatment target and normal tissues were estimated on plain X-rays using bone landmarks or contrast given at the time of simulation and were drawn by hand inside the outline of the external surface. The error introduced by these multiple points of uncertainty was corrected by increasing the size of the irradiated volume in order to guarantee that the tumor would be treated. Widespread availability of whole-body CT scans led to improved knowledge of the anatomic locations of tissues. However, planning typically was still performed on a few contours, which were used to represent the entire volume.

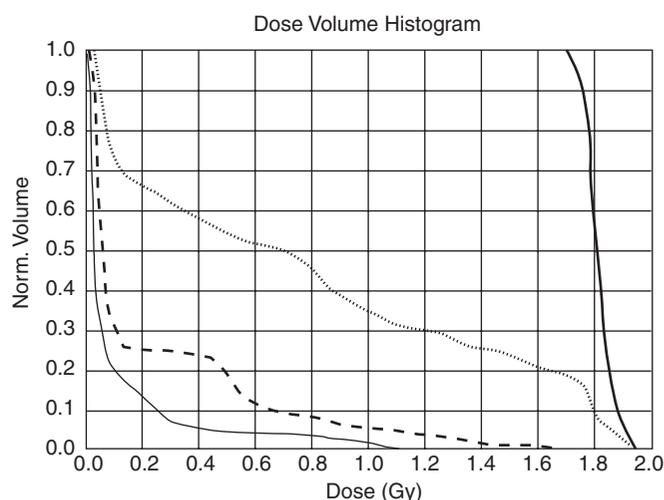
With three-dimensional conformal RTP, the individual slices of a CT scan, including both the external shape and any internal structures, can be reconstructed into a complete three-dimensional representation (4). By projecting the relationship of internal structures along the axis of a proposed radiation field, a beam’s-eye view can be displayed (Figure 7-1). This is particularly useful in planning

**FIGURE 7-1**

Beams-eye-view display of a patient with a cholangiocarcinoma treated with 3D conformal external beam radiation therapy. One of the three fields in antero-posterior direction is shown. The tumor is marked as gross tumor volume (GTV). The planning target volume (PTV) is not shown, but is necessary to ensure adequate dose delivery to the GTV and surrounding microscopic tumor tissue. The PTV margin depends on the positioning variability and the positioning insecurity due to internal organ movements.

radiation beams outside the axial plane. 3D treatment planning requires a standardized approach in order to derive an optimal portal field. The algorithm for defining the beam portal size is based on Report 62 from the International Commission on the Reporting of Units (ICRU) (5). On a radiological imaging device used for planning, the first step is contouring the visible tumor target (GTV or gross tumor volume). A defined margin surrounding the GTV, the tissue with probable microscopic involvement, should be defined, resulting in the clinical target volume (CTV). CTV and GTV are disease-determined parameters that cannot be altered by any improved treatment techniques, including positioning, stereotactic treatment, or intensity-modulated techniques. Additional margin, derived from positioning inaccuracy, is called the set-up margin. Internal organ movements define the internal target volume (ITV). The set-up margin added to ITV results in the planning target volume (PTV).

Three-dimensional conformal RTP tools also can calculate the volume of any structure and the distribution of radiation dose within that volume. This information can be displayed as a dose-volume histogram, which is a summary of the three-dimensional dose distribution for a particular structure (6). A dose-volume histogram (DVH) is calculated by dividing the structure of interest into a number of volume elements (voxels). The liver is divided into approximately

**FIGURE 7-2**

Example of cumulative dose-volume histogram for the proposed treatment plan for the patient in Figure 7-1. Cumulative dose-volume histograms for the liver and both kidneys are shown. The figure displays the fractional volume of normal tissue (ordinate) that receives radiation greater than or equal to a specified single dose fraction (abscissa). The thick line is planning target volume (PTV). The dotted line indicates exposure of the liver. The long dash line shows exposure of the right kidney, and the solid line shows exposure of the left kidney.

2000 to 2500 voxels. The dose received by each voxel is determined and displayed as a plot, called the DVH (Figure 7-2).

The volumetric information also has been used to develop models that attempt to predict the risk of an individual patient developing a particular complication (7). These models have particular promise when RT is delivered to only a portion of an organ; the risk of a complication with whole-organ radiation is fairly well known.

Application of Three-Dimensional RTP to Intrahepatic Cancers

RTP offers three key improvements over previous planning methods with regard to liver irradiation. First, the definition of the target volume for RT is much more reliable with the direct integration of CT scans into the planning process than are clinical estimates of tumor location using bone landmarks. Second, use of radiation fields outside the axial plane and beam's-eye view displays could minimize normal liver irradiation while ensuring coverage of the target volume. Third, three-dimensional RTP could quantify the relationship of dose and volume within the liver achieved by any particular radiation plan, allowing a systematic approach to escalating the dose of RT to amounts higher than the whole-liver tolerance dose.

Because the risk of RILD, the major dose-limiting complication, is directly related to the volume of normal liver irradiated, all investigation should use volumetric criteria to

assign the radiation dose. The CTV margin for hepatocellular carcinoma and liver metastasis can be between 0.5 and 1.0 cm. The CTV for patients with centrally located cholangiocarcinomas also includes an additional 1 to 2 cm of the biliary tract, both proximal and distal to the tumor. Although the liver is subject to considerable movement variability due to respiration, the PTV margin can be significantly adjusted and some authors have reported improved PTV margins using better immobilization and beam application coordinated with breathing movements (8). Liver positioning variability in the longitudinal direction is greater than in the transversal plane, and 0.6 to 1.0 cm in the transversal plane and 1.0 to 1.5 cm in the longitudinal plane for PTV margin are sufficient in most cases (9,10). In individual cases, though, margins must be corrected for breathing-associated position variability, such as displacements of up to 2.1 cm in the cranio-caudal direction, 0.8 cm in the ventro-dorsal direction and 0.9 cm in the left-right directions (11). Furthermore, isocenter matching with a CT simulation prior to each treatment session allows further reduction of PTV margins to 0.5 cm (11). The normal liver is defined for the dose-volume histogram calculation as the outline of the liver minus the radiographically abnormal area(s) seen on CT scan. During the planning process, possible RT plans are compared and the best plan is selected based on the most appropriate dose-volume histogram. The total dose of RT delivered to nontarget tissue should always be documented using a dose-volume histogram (Figure 7-2).

Although 3D treatment planning represents a major step forward by using volumetric criteria to determine the RT dose, it does not take advantage of all of the dose-volume data, and patients with considerably different complication risks could receive the same doses. The current approach assigns an individualized dose to a particular patient using the volumetric data accumulated from previous experience. Patients in current practice now can be assigned as having a risk of RILD, and the total dose of RT associated with that risk can be calculated and delivered.

Intensity-Modulated Treatment Planning

In the field of external beam radiation, some improvement of RT can be expected from intensity-modulated radiation treatment (IMRT) as compared to 3D conformal radiation therapy. (Figures 7-3a and 7-3b). Volume definitions of CTV and PTV for optimal IMRT planning remain the same as for 3D treatment planning. Using non-coplanar three to seven fields, concave dose distributions can be achieved. Adapted beam profiles result in reduced portal field sizes (compare Figure 7-3c to Figure 7-3d). An improved dose distribution may lead to less radiation applied to nontarget tissue. The case in Figures 7-3a and 7-3b illustrates the difference between 3D conformal treatment planning and IMRT in a patient with cholangiogenic liver cancer treated with 45 Gy prior to liver transplantation. IMRT-based radiation therapy minimizes the dose applied to the liver and

right kidney (Figures 7-3e and 7-3f). Overall, the benefit of IMRT in the treatment of liver or liver bed tumors seems small and using more than three portal fields does not improve the dose distribution to liver, because most of the target volumes are roundly shaped. Nevertheless, dose delivery optimization might be relevant in cases when definitive focal radiation therapy is used with doses up to 70 Gy, allowing some normal liver tissue to be saved by virtue of reduced margin geometry.

PRIMARY HEPATOCELLULAR CARCINOMA AND CHOLANGIOCARCINOMA

A dose response of hepatocellular carcinoma to ionizing radiation is well established; radiological responses are rare if the dose is less than 40 Gy (12). The series of studies performed by the Radiation Therapy Oncology Group provides important information on the use of RT with hepatocellular carcinoma (HCC) (13-15). Whole liver RT (21 to 24 Gy) was combined with concurrent intravenous chemotherapy. Later studies followed this regimen with radiolabeled antiferritin every 2 months. Response rates, using volumetric computed tomography (CT) criteria, were approximately 20% with whole liver RT and chemotherapy and 48% after radiolabeled antiferritin. The median survival rate was 4.9 months for all patients. Some subgroups had a considerably longer median survival rate, such as previously untreated alpha-fetoprotein-negative patients, who had a median survival rate of 10.5 months. A similar regimen has also been studied for patients with intrahepatic cholangiocarcinoma (16). A total of 24 patients were given radiolabeled anticarcinoembryonic antigen (anti-CEA) after a course of whole liver RT (21 Gy) and intravenous chemotherapy. The anti-CEA and chemotherapy were repeated every 2 months. Repeated assessment of the response rates, which were judged using volumetric criteria, were 14% for whole liver RT and chemotherapy, and increased to 24% after radioimmunoglobulin treatment. Although the median survival rate was 10.1 months, which was higher than in a previous study at the same institution, all patients had expired by 2 years.

In the most recent phase II trial from the University of Michigan, dose escalation to focal liver regions with either hepatobiliary tumors or liver metastasis was used (9). Radiation was applied twice daily using 1.5 Gy fraction dose for tumors with a median tumor load of 0.8 dm³. The treatment was administered with the radiation sensitizer fluorodexyuridine, which was given through the hepatic artery at a dose of 0.2mg/kg body weight per day. A first treatment period of 12 days was interrupted by a treatment interruption of 14 days, followed by a second treatment period of 14 days. Doses up to 90 Gy have been given if sufficient normal liver could be spared.

Transcatheter arterial chemoembolization can be used for nonresectable hepatocellular carcinoma. If radiation is

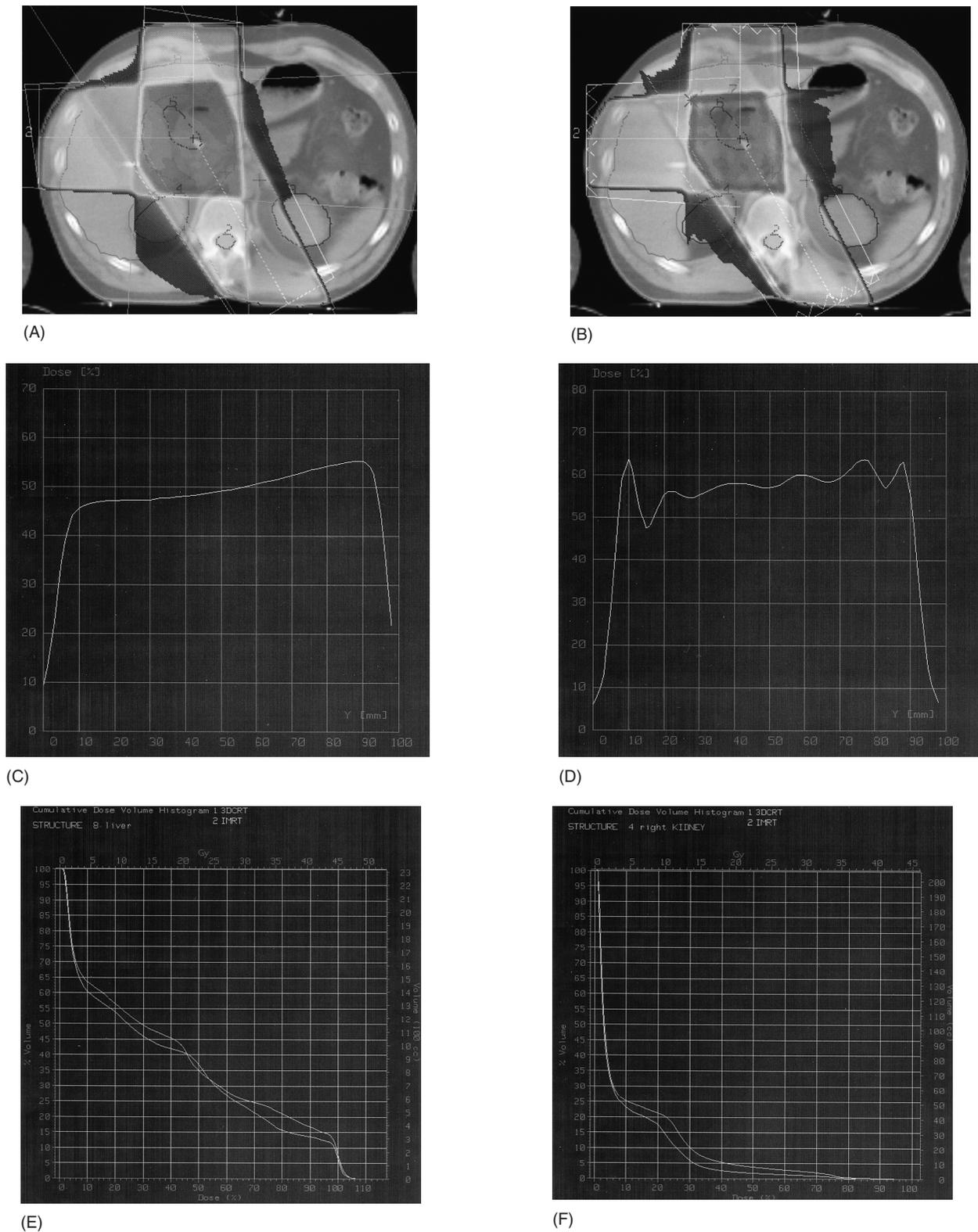


FIGURE 7-3

A 36-year-old patient suffering from cholangiocarcinoma was treated with external beam radiation to a dose of 45 Gy in single dose fractions of 1.8 Gy followed by orthotopic liver transplantation. (A) shows the beam geometry as it was used in the 3D-conformal radiation treatment compared to an IMRT-based external beam treatment planning in (B). The major differences lie in the beam profile, which is flat in 3D-conformal RT (C) compared to the irregular shape of the beam profile in IMRT (D). Intensity modulation results in unchanged dose distribution to the target volume (PTV), minimizing the radiation dose delivered to the liver and kidneys (E and F).

added, external beam radiation with fractions of 1.8 to 2.0 Gy/day have been used up to a dose of 40 to 50 Gy (17,18). Currently, it remains unclear whether external radiation therapy improves the outcome of chemoembolization (18).

Brachytherapy has not been used for HCC or intrahepatic cholangiocarcinoma, although there has been considerable experience with intraluminal brachytherapy for proximal extrahepatic bile duct cancers (19,20). Overall median survival rates using brachytherapy combined with external beam RT range from 10 to 24 months, with 3-year survival rates of 10 to 30%. Despite the ability to deliver a very high total dose of ionizing radiation locally with brachytherapy, progression of local disease is still common. This finding may be attributable to the rapid decrease in dose with distance from the intraluminal catheter, such that a tumor located 2 cm from the catheter will receive only about one-quarter of the dose.

The use of yttrium-90 (90Y) microspheres applied through the hepatic artery has been proposed for the treatment of unresectable hepatocellular carcinoma (21). This approach achieves a response rate of 20%, comparable to external beam radiation. Doses of 100 Gy are delivered, based on MIRD calculations. These doses cannot be compared directly to external beam doses because of different dose rate. It seems that the tumor-to-liver activity uptake ratio might be important for significant response rates.

There is no proven benefit of adjuvant RT after partial hepatectomy, even though up to two-thirds of patients develop an intrahepatic recurrence in cases of hepatocellular and cholangiogenic tumors. This may be attributable to growth of tumor at the edge of the previous resection, presumably a local recurrence, or growth of disease elsewhere in the liver, representing either metastatic disease or a new primary cancer. In view of the finding that up to two-thirds of patients develop an intrahepatic recurrence, it would be appropriate to evaluate the role of adjuvant RT or chemotherapy, or both, for high-risk patients after partial hepatectomy for HCC or intrahepatic cholangiocarcinoma. Experiences with adjuvant radiation therapy are limited and mostly are not in favor of postoperative radiation therapy (22). Others have proposed the use of intraoperative radiation therapy in selected cases of patients with main hepatic duct carcinoma (23).

METASTATIC COLORECTAL CANCER TO THE LIVER

Whole liver RT can produce palliation of pain in approximately one-half of symptomatic patients, although it is often accompanied by nausea/vomiting and fevers/night sweats (2). Objective response rates are less than 10%, and median survival rates are 2 to 4 months (2,24). Combinations of whole liver RT and systemic or regional chemotherapy have resulted in improved response rates and survival (25), although the differences could be related to the selection bias of chemotherapy-containing trials.

One method of delivering a higher dose of radiation to the liver is through the use of yttrium-90 (90Y) microspheres. 90Y is a pure beta radiation emitter with a half-life of 64.5 hours and an average electron range of approximately 2.5 cm. The microspheres are infused into the hepatic artery as a form of regional therapy for well vascularized tumors. Although 90Y microspheres are promising, a considerable amount of research into technical issues must be done before this type of RT can be used routinely.

Brachytherapy techniques, either permanent or temporary, are also capable of delivering high doses of radiation to selected portions of the liver. Brachytherapy after resection of liver metastasis from colorectal carcinoma has been shown to be feasible using an interstitial application of 30 Gy with an afterloading system using high-dose iridium-192 intraoperatively (26). Although these techniques are promising, the relative disadvantages of brachytherapy are the need for an open surgical procedure and the difficulty of obtaining good distribution of the RT dose with tumors larger than 3 to 5 cm.

Postoperative systemic treatment with 5-fluorouracil in the presence of nonmeasurable hepatic disease was investigated by the ECOG in combination with external beam therapy to the liver (27). Radiation was applied to the whole liver with 10×2 Gy. The median time to treatment failure was 8.3 months in the patients who received radiation therapy to the liver. This was not significantly different from those patients given postoperative systemic treatment alone, who had a median time to treatment failure of 6.8 months.

RESULTS OF THREE-DIMENSIONAL RTP FOR NONHEPATIC TUMORS

Considerable interest has developed regarding the use of three-dimensional RTP for other tumors. One example is prostate cancer, with the goal of dose escalation without increasing the risk of developing a severe complication of the rectum. To date, treatment using three-dimensional RTP has demonstrated acceptable acute and chronic toxicity and good biochemical control in a favorable subset of patients, approaching the toxicity and control of surgical therapy for the same group (28). There are, however, some key differences between three-dimensional RTP for prostate cancer and 3D RTP for hepatic tumors. The major difference is that the dose-limiting structure for prostate cancer is an adjacent organ, the rectum, whereas the liver itself is the dose-limiting structure for hepatic tumors. Also, the entire prostate is usually designated as the target volume, and all patients are treated to the same dose, regardless of the volume of rectum included in the field. Thus, three-dimensional RTP for prostate cancer has been used to

benefit targeting and field design, but without using the volumetric studies.

Lung cancer is located within the major dose-limiting structure, the lung itself, and the risk of a complication is related to the volume of normal lung irradiated. Also, the whole-organ tolerance of the lung is well below the dose required to control gross disease. Thus, the experience with lung cancer is closer to that of liver tumors. Although work in this area is preliminary, the experience to date has shown that some patients could be irradiated at doses well over 50% higher than traditional doses without developing radiation pneumonitis (29).

RESULTS OF TREATMENT

Three prospective trials dosing volumetric criteria to determine the optimal dose of ionizing radiation prescribed were reported. Patients were eligible to receive up to 72.6 Gy, well over twice the whole-liver tolerance dose, depending on the fractional volume of normal liver irradiated. Radiation therapy was combined with hepatic arterial fluorodeoxyuridine (0.2 mg/kg/day), based on the known pharmacological advantage of hepatic arterial chemotherapy and preclinical evidence that fluorodeoxyuridine is a potent radiation sensitizer (30). Access to the hepatic artery was usually gained by means of a temporary brachial artery catheter, which could be safely maintained for 2 to 21 weeks. Patients receiving more than a whole-liver dose of RT, therefore, required two placements of the hepatic artery catheter with a 2-week rest between placements (Figure 7-4).

In a pilot study at the University of Michigan, 33 patients were treated, of whom 13 received boost doses of 45 or 60 Gy with a whole-liver dose of 30 Gy (31). The concept of administering an initial 30 Gy to the whole liver, followed by a boost to the abnormal areas, was patterned after the standard RT concept of a “shrinking field” technique, in which a lesser dose of RT is delivered to areas

thought to harbor subclinical disease while gross disease receives the full dose. From this experience we learned that a high dose of RT could be delivered safely to partial volumes of the liver, with a high response rate and acceptable toxicity. The analysis of the pattern of failure, however, suggested that irradiation of the whole liver was not necessary. Therefore, the shrinking field technique was abandoned in subsequent trials.

In a second series, a total of 48 patients—consisting of 22 patients with intrahepatic metastases from colorectal cancer, 17 with HCC, and 9 with intrahepatic cholangiocarcinoma—were treated (32). Half of the patients received 48.0 to 52.8 Gy, and the other half received 66.0 Gy to 72.6 Gy. There was no difference in the response rate in respect to the dose applied. The median survival time was 16 months, with an actuarial 4-year survival of 20%. Importantly, liver outside the high dose radiation fields retained the ability to hypertrophy, comparable to postsurgical hypertrophy (Figure 7-4).

In the most recent series, patients were treated with continuous fluorodeoxyuridine and focal radiation therapy to intrahepatic primary tumors and metastases of colorectal carcinoma (9). All radiation was given at 1.50 to 1.65 Gy twice a day, resulting in a total dose applied ranging from 40.5 to 90.0 Gy, which was significantly higher than the dose that would have been delivered by the previous protocol. Only 1 of the 43 patients developed RILD, which did not differ significantly from the predicted 10% risk of complication (95% confidence interval of 0 to 22%), supporting the predictive ability of the model. The most significant nonhepatic toxicity was upper gastrointestinal bleeding, observed in 7% of patients. Biliary stricture also was reported in 5% of patients. Dose escalation up to 70 Gy seemed to be of benefit to patients, resulting in a median survival time exceeding 16 months, compared to those treated with lower doses who achieved a median survival time of 12 months. Compared to previous observations, (29) the median progression-free survival time was similar for patients with colorectal carcinoma liver metastases and primary hepatobiliary cancer (Figure 7-5).

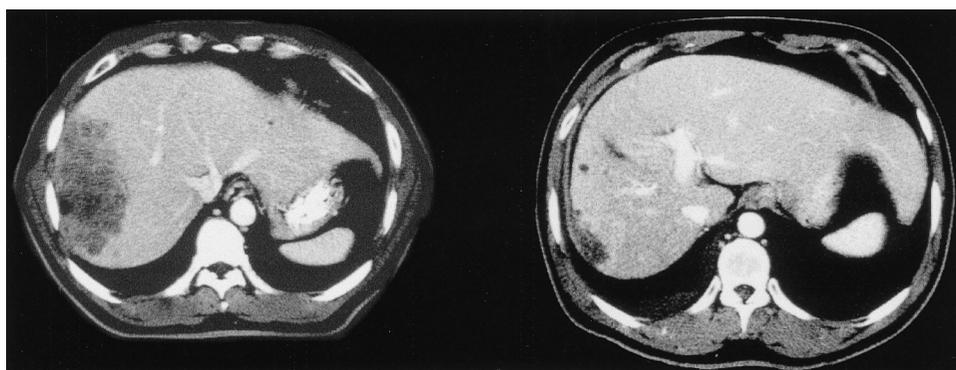


FIGURE 7-4

Treatment schedule of external beam radiation in combination with twice daily external beam application.

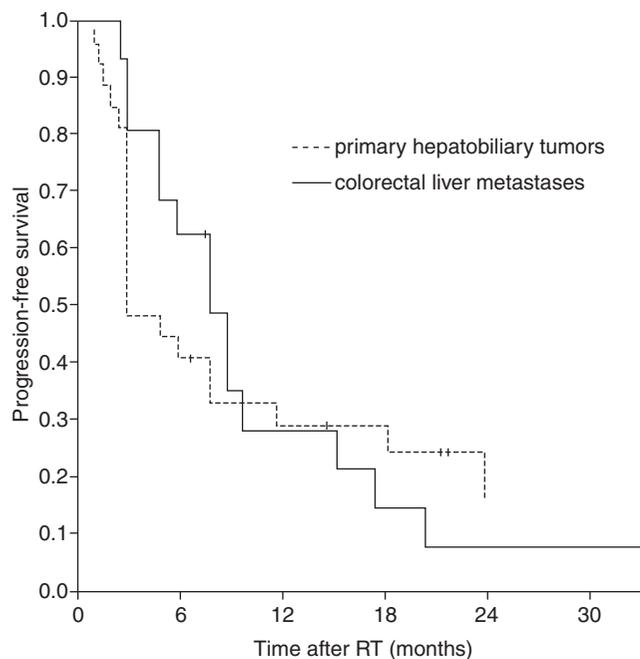


FIGURE 7-5

A patient with voluminous metastatic disease from colorectal carcinoma to the right liver lobe was treated with combined chemoradiation, resulting in prolonged progression-free survival. There is remarkable compensatory hypertrophy of the left lobe.

COMPLICATIONS OF TREATMENT

Most of the acute toxicity of therapy has been observed in patients receiving whole liver radiation. Of those receiving partial liver RT, only about 10% developed toxicity of grade 3 or higher during treatment (32,33). RILD requiring medical support was observed in 1 of 44 patients treated with doses above 48 Gy. In contrast, it was common for radiographic changes in the liver to occur within the area of high radiation dose. Nausea and vomiting were common, but usually only when radiation was given directly to the stomach in order to irradiate portions of the left lobe of the liver. Similarly, gastritis and/or upper abdominal pain also occurred only when portions of the stomach were necessarily irradiated. Fatigue was common in patients receiving RT to large volumes of the liver. Hematologic toxicity usually was grade 1 or 2, and improved after the treatment was completed. Grade 1 or 2 changes in hepatic enzymes were also common and had no obvious relationship to the development of RILD. The most common subacute toxicity was gastric/duodenal bleeding, which occurred in up to 13% of patients (9,31–34). Typically, this required a transfusion, but not surgical intervention. RILD was also seen, but has been rare since the treatment was modified to exclude whole liver RT in patients receiving focal irradiation.

COMPARISON WITH COMPETITIVE THERAPIES

The long-term hepatic control rate of 50% observed with high-dose RT and hepatic arterial fluorodeoxyuridine for patients with primary hepatobiliary tumors compares well with results of other treatments in the literature, in which hepatic progression was the most common site of failure after resection of HCC and after RT for cholangiocarcinoma (19). Few other data are available for comparison, as other studies failed to report either the patterns of failure or freedom from hepatic progression. This is especially true for patients with tumors > 6–10 cm in diameter, who are typically the ones receiving radiation.

The median survival time of 16 months for patients with primary hepatobiliary tumors was superior to that reported for RT alone, similar to a trial of long-term hepatic arterial chemotherapy, and approached the results of resection (19). Although these findings are encouraging, patient selection factors, as with all single-arm studies, may have contributed to the results observed.

The results of high-dose RT using three-dimensional RTP or IMRT for this group of patients, most of whom had received previous 5-fluorouracil-based chemotherapy and some transarterial chemoembolization, are favorable when compared with second-line systemic chemotherapy or whole-liver radiation with or without chemotherapy (35). Long-term hepatic arterial fluorodeoxyuridine alone, as a first-line therapy, can produce objective responses in 40 to 60% of patients, with a median survival rate of 12 to 17 months (36). This suggests that focal radiation therapy and long-term hepatic artery chemotherapy may be viewed as complementary treatments and it may be possible to combine the two, as has been reported after surgical resection (37).

FUTURE DIRECTIONS IN TREATMENT

Several recent advances may be useful for improving the results of RT for liver tumors. For example, because the safe dose of radiation is highly dependent on the volume of normal liver irradiated, treatment techniques that decrease the target volume are useful. In a previously described approach, the target volume was increased in both the cranial and caudal dimensions in order to account for liver motion caused by breathing. Thus, elimination of this correction may spare large volumes of normal liver, and could be accomplished by either gating RT or, more simply, using breath-holding techniques (8,38). Research in both of these areas is in progress. Further reductions in the volume of liver that is irradiated could be accomplished with improved definition of the target volume through better imaging.

The more standard use of radiation sensitizers or radioprotectors may also improve the outcome of treatment

for patients with intrahepatic cancer (30,39). Aside from the use of fluoropyrimidines, other sensitizers such as the thymidine analogues bromodeoxyuridine and iododeoxyuridine, as well as other nucleosides such as gemcitabine and cisplatin, have also been considered. Furthermore, novel agents targeting tumor-specific growth pathways, such as the epidermal growth factor receptor-defined signaling pathways with Cetuximab® or Iressa® might be useful in combination with radiation. Sensitizers are particularly attractive for the treatment of liver tumors given that the dual blood supply of the liver permits the selective perfusion of tumors by means of hepatic arterial circulation. Similarly, infusion of radiation protectors, either intravenously or in the portal vein, may be able to provide selective protection of the normal liver, as has been shown in preclinical studies (40).

Another area of study is the process of RILD. Although the lack of an animal model has slowed research in this area, recent data suggest that cytokines such as transforming growth factor β may at least participate in the process leading to veno-occlusive disease. Aggressive thrombolytic therapy is currently under study for the veno-occlusive disease observed after bone marrow transplantation (41), and it is possible that this approach may be useful in preventing the development of RILD as well.

In summary, combinations of better dose delivery, improved imaging of intrahepatic cancer, more effective use of radiosensitizers and eventually radioprotectors, and elucidation of RILD may lead to improved outcome of treatment for patients with unresectable intrahepatic cancer.

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